

Targeted magnetic delivery of Cells with an MRI scanner

J. Riegler^{1,2}, J. A. Wells¹, P. Kyrtatos¹, A. N. Price¹, and M. F. Lythgoe¹

¹Centre for Advanced Biomedical Imaging (CABI), Department of Medicine and Institute of Child Health, University College London (UCL), London, United Kingdom, ²Centre for Mathematics and Physics in the Life Sciences and Experimental Biology (CoMPLEX), UCL, London, United Kingdom

Introduction

One of the challenges in the biomedical sciences is to develop concurrent MR imaging and targeting of labelled cells in the body. In recent years the use of cells to repair damaged tissue has led to only modest success, in part due to low uptake at the site of injury². Cell therapies would greatly benefit from methodologies aimed at targeting cell traffic. Magnetic delivery has been proposed for localized delivery. Permanent magnets placed outside of the body have been used for magnetic delivery in animal models³⁻⁶ and clinical trials⁷. However the fast decay of magnetic forces with increasing distance from the external magnet restricts the applicability of this approach to tissues or organs which are close to the body surface.

High performance MR gradient coils produce homogeneous magnetic field gradients that penetrate the whole body. Work by other groups has shown that these field gradients are strong enough to move magnetic objects inside the scanner^{1,8,9}. A clinical 1.5T system has been used to image and navigate a 1.5mm diameter ferromagnetic bead in a flow-isolated swine artery⁹. In addition, a recent phantom study showed that dedicated gradient coils could divert magnetic ferrofluid as proof of principle for selective deposition of intravascular particles¹.

In this work we demonstrate for the first time the feasibility of targeted cell delivery by steering magnetically labelled stem cells using MR imaging gradients in a vascular bifurcation flow model. Our initial findings support the potential value of MRI for improved targeting of intravascular cells.

Methods

Theoretical modelling indicated the feasibility of moving cells with the field gradients provided by the gradient coils of a high field MRI system. We therefore created a model for a bifurcation of a small artery. Experiments were performed using a custom designed vascular bifurcation model (see Figure 1), connected to an infusion pump (Harvard Instruments PHP2000). The bifurcation was placed into the centre of a 9.4T experimental scanner (Varian, 60 mm bore size, gradients: rise time $5 \text{ T m}^{-1} \text{ ms}^{-1}$, max. 1T/m), with the direction of flow parallel to B_0 (Z). Human mono nuclear cells were



labelled with nanometre or micrometer sized super paramagnetic iron oxide particles Endorem (\varnothing 200nm) or Bangs Particles (\varnothing 1.5 μm). 0.5 ml of labelled cells (2×10^6 cells/ml) were infused at flow rates of 0.06 ml/min to 1.8 ml/min leading to a mean velocity of 0.2cm/s to 6 cm/s whilst gradients (amplitude 500mT/m) were applied in the X direction, perpendicular to the direction of flow. Gradients were pulsed due to hardware limitations (2ms on, 7ms off). The cell suspensions leaving each bifurcation outlet tubes (volume 0.25ml each) were collected and cell concentrations were estimated using a haemocytometer. The direction of the gradients was then reversed and 0.5ml cell suspension was infused as before. The process was repeated three times for each direction.

Figure 1: The model bifurcation used in these experiments. The bifurcation was manufactured by AG prototypes using CNC milling techniques. The inner diameter was 0.8mm and the bifurcation angle was 30° .

Results

Following application of the magnetic field gradient from the MRI system, there was up to 50% increase in the number of cells reaching the outlet to which the gradients were directed. This was apparent for both gradient directions (Figure 2). Steering of cells to one outlet tube led to a susceptibility increase which could be seen on gradient echo images.

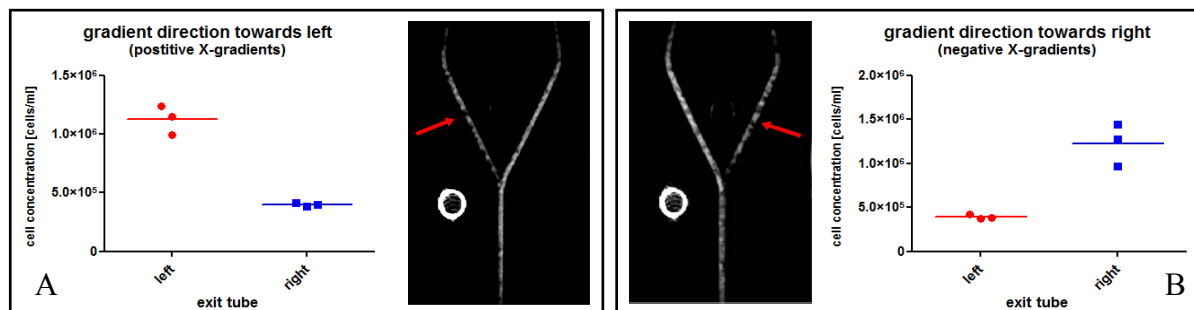


Figure 2: Diagram A and B show the cell concentrations at the exit tubes following application of positive (A) and negative (B) X gradients for cells labelled with Bangs Particles at a flow rate of 1 cm/s. Gradient echo images show a reduced signal intensity in the exit branch to which the cells were directed (red arrow) (TE 1.24 ms, TR 100 ms, FA 30°, FOV 50x30 mm, Matrix 192x128).

Conclusions

Our results show that a MRI scanner can be used to steer cells into the desired direction in a vascular bifurcation model. We also show the possibility of using MR imaging to confirm targeting success. These initial findings provide evidence to support the potential of magnetic targeting of cells using MRI for future clinical applications, allowing image guided targeted delivery of cells and other therapeutic agents to sites of the body which cannot be reached with external permanent magnets. This approach could improve localization and simultaneous monitoring of cells in organ systems such as the liver or the brain and may prove complementary to the systemic injection of cell therapies, thus expanding the role of stem cell therapies.

References: [1]. J. B. Mathieu, S. Martel, *Biomedical Microdevices* **9**, 801 (2007) [2]. J. C. Roth, D. T. Curiel, L. Pereboeva, *Gene Ther* **15**, 716 (2008). [3]. J. P. Fortin-Ripoche et al., *Radiology* **239**, 415 (2006). [4]. Hui-Li Ma et al., *Journal of Biomedical Materials Research Part A* **84A**, 598 (2008). [5]. P. G. Kyrtatos et al., *JACC: Cardiovascular Interventions* **2**, 794 (2009). [6]. D. Suman, P. Vishwesh, F. William, K. Ban-An, B. C. Robert, *Cancer Science* **100**, 1537 (2009). [7]. A. S. Luebke, C. Alexiou, C. Bergmann, *Journal of Surgical Research* **95**, 200 (2001). [8]. N. J. Darton et al., *Nanotechnology* **19**, 395102 (2008). [9]. S. Martel et al., *Applied Physics Letters* **90**, 114105 (2007).